AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 8 October 1984

IN THIS ISSUE

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13-CIS RETINOIC ACID THERAPY FOR KAPOSI'S SARCOMA

13-cis retinoic acid (RA), a metabolite of vitamin A with potent biologic activity, has been used clinically for treatment of severe acne and for the chemoprevention of cancer (Peck GL, Olsen TG, Yoder FW, et al: N Engl J Med., 1979, 300:329-333; Elias PM, Williams ML: Arch Dermatol., 1981, 117:160-180). In addition to its effects on cellular differentiation, RA inhibits virus induction (Yamamoto N, Bister K, ZurHausen H: Nature, 1979, 278:553-554) and potentiates the T cell immune response (Lotan R: Biochim Biophys Acta, 1980, 605:33-91). For these reasons, we thought that RA might be useful in treating Kaposi's sarcoma (KS) associated with AIDS, and a pilot trial was begun in March, 1983.

Six patients received RA by mouth in a daily dose of 2.0 mg/kg. All were young homosexual men with biopsy-proven cutaneous KS who gave informed consent to the study. Each patient was monitored weekly for tumor response and possible drug toxicity. We considered 4 weeks of continuous therapy as an adequate trial.

The results of this study are shown in the table. All patients developed the expected desquamative dermatitis. It became necessary to discontinue the drug in patients 4, 5, and 6. While on therapy, two patients (1 and 4) developed oral lesions typical of those caused by Herpes simplex virus. One patient (5) developed Pneumocystis carinii pneumonia. These infections are typically associated with AIDS and were not attributed to RA toxicity. No patient exhibited tumor regression, and all adequately-treated patients developed new lesions during the trial.

We conclude from this pilot study that RA is not an effective drug for treating KS associated with AIDS and that the skin toxicity which was produced by RA at the dose used made it an unacceptable drug for this group of patients.

CIS-RETINOIC ACID THERAPY FOR KAPOSI'S SARCOMA

Patient	Duration of Therapy (Wk)	Response	Toxicity
1	12	Progression	Cutaneous
2	4	Progression	Cutaneous
3	4	Progression	Cutaneous
4	3	Progression	Cutaneous
5	1	—	Cutaneous
6	1	—	Cutaneous

J. L. Ziegler, F. A. Volberding, and L. M. Itri. Veterans Administration Medical Center; San Francisco General Hospital, University of California; San Francisco, California 94121; Hoffman-LaRoche, Inc., Nutley, New Jersey 07110.

SIMIAN AIDS: AN OVERVIEW

An immunosuppressive disease which resembles human AIDS has recently been recognized among Macaca monkeys housed at several regional primate centers in the United States (Henrickson RV, Osborn KG, Madden DL, et al: Lancet, 1983, 1: 388-390; Hunt RD, Blake BJ, Chalifoux LV, et al: Proc Natl Acad Sci USA., 1983, 80:5085-5089; Stromberg K, Benveniste RE, Arthur LO, et al: Science, 1984, 224:289-292). Like human AIDS, the simian disease, SAIDS, is characterized by profound immunosuppression, mul-

tiple opportunistic infections, chronic wasting, in some instances malignancy, and a high rate of mortality (Henrickson RV, Osborn KG, Madden DL, et al: Lancet, 1983, 1:388-390; Hunt RD, Blake BJ, Chalifoux LV, et al: Proc Natl Acad Sci USA., 1983, 80:5085-5089; Stromberg K, Benveniste RE, Arthur LO, et al: Science, 1984, 224:289-292; London WT, Madden DL, Gravell M, et al: Lancet, 1983, 2:869-873; Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76; Letvin NL, King NW, Daniel MD, et al: Lancet, 1983, 2:599-602). Some affected monkeys have developed transitory skin lesions which are histopathologically similar to the "patch" and "plaque" lesions of Kaposi's sarcoma seen frequently in human AIDS patients (London WT, Madden DL, Gravell M, et al: Lancet, 1983, 2:869-873). Because of the similarities in the clinical and pathological features of the human and simian diseases, studies of SAIDS, particularly those concerned with vaccination and treatment, may increase our understanding of and contribute to the control of human AIDS.

SAIDS has been experimentally transmitted to healthy rhesus monkeys (Macaca mulatta) by inoculations of unfiltered homogenates of tissues, whole blood, and serum from rhesus monkeys with advanced disease (Hunt RD, Blake BJ, Chalifoux LV, et al: Proc Natl Acad Sci USA., 1983, 80:5085-5089; London WT, Madden DL, Gravell M, et al: Lancet, 1983, 2: 869-873; Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76; Letvin NL, King NW, Daniel MD, et al: Lancet, 1983, 2:599-602). Direct evidence implicating a virus as the causative agent of SAIDS first came from experiments in which the disease was transmitted to healthy juvenile rhesus monkeys using as an inoculum a cell-free filtrate of plasma or a homogenate of lymphomatous tissue from diseased animals (Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76; Letvin NL, King NW, Daniel MD, et al: Lancet, 1983, 2:599-602). The pore size of the filters used in these studies was small enough to exclude free-living microorganisms.

More recently, we and others have reported that a type D retrovirus, related but not identical to Mason-Pfizer monkey virus (MPMV) (Chopra HC, Mason MM: Cancer Res., 1970, 30:2081-2086), the prototype of type D retroviruses, is the causative agent of SAIDS (Gravell M, London WT, Hamilton RS, et al: Lancet, 1984, 1:334-335; Marx RA, Maul DH, Osborn KG, et al: Science, 1984; 223:1083-1086). The p27 core polypeptide of MPMV was found by competition radioimmunoassay (RIA) to be antigenically closely related to the core polypeptide of the SAIDS retrovirus. However, antigenic differences existed between the envelope glycoprotein, gp70, of MPMV and that of the SAIDS retrovirus (Marx RA, Maul DH, Osborn KG, et al: Science, 1984; 223:1083-1086). The reverse transcriptases of the SAIDS retrovirus and of MPMV were also found to have similar characteristics (Colcher D, Schlom J: Biochim Biophys Acta, 1980, 607:445-456). Both showed a Mg^{++} preference with the synthetic templates poly(rA)·oligo$(dT)_{12-18}$ and poly(rC)·oligo$(dG)_{12-18}$ but a Mn^{++} preference with poly$(rC)_n$·oligo$(dG)_{12-18}$ (Gravell M, London WT, Hamilton RS, et al: Lancet, 1984, 1:334-335).

In our studies, SAIDS was transmitted to two healthy rhesus monkeys (E-247 and B-959) by inoculating them at the National Institute of Neurological and Communicable Disorders and Stroke with an isolate of the SAIDS retrovirus, IDB-1, from serum of rhesus monkeys which developed fatal SAIDS while housed at the California Primate Research Center

at the University of California at Davis (CPRC) (Gravell M, London WT, Hamilton RS, et al: Lancet, 1984, 1:334-335). The virus isolation was made in rhesus monkey primary bone marrow cultures. Prior to use in transmission studies, the isolate was passed four times in vitro in low-passage normal rhesus monkey fibroblasts and purified by discontinuous and continuous density gradient centrifugation in neutral sucrose (density 1.15-1.17 gm/cm^3). Fractions pooled for the inoculum showed peak absorbance at 254 nm and contained the reverse transcriptase activity. Only type D retrovirus particles were seen by electron microscopy in negative stains of the inoculum. Finally, in an RIA broadly reactive for type C virus of Colobus monkeys, CPC-1, and using specific antisera to purified core proteins of several type C retroviruses, no evidence was found that the virus inoculum was contaminated with type C retroviruses (L. O. Arthur, unpublished data).

Both of the inoculated monkeys developed early manifestations of SAIDS (neutropenia, lymphadenopathy, and splenomegaly) between 2 and 4 weeks after inoculation. More severe disease was noted in monkey E-427, and an enlarged right inguinal node was removed from this animal for histopathological examination 5 weeks after the experimental inoculation. The normal architecture of the nodular cortex was found to be effaced by extensive atypical proliferation of lymphoblasts and immunoblasts. A few subcapsular aggregates of small lymphocytes provided the only evidence of follicles. Plasma cells were rarely seen. This histopathology is consistent with that seen in previously studied animals with SAIDS in early-to-intermediate stages of disease. Both animals died 8 weeks after inoculation with diseases similar both clinically and pathologically to the disease described previously in experimentally and naturally infected rhesus monkeys with SAIDS (Henrickson RV, Osborn KG, Madden DL, et al: Lancet, 1983, 1:388-390; Hunt RD, Blake BJ, Chalifoux LV, et al: Proc Natl Acad Sci USA., 1983, 80:5085-5089). Death in both animals was attributed to pneumonia caused by an opportunistic invader, probably a virus.

The antibody responses in the two monkeys to the SAIDS virus were monitored by an enzyme-linked immunosorbent assay. No significant increase in IgG antibody to SAIDS virus was detected in serum samples taken from these animals at various intervals during the 8 weeks they lived after infection. Other rhesus monkeys infected with and showing titers of antibodies to cytomegalovirus (CMV) or simian adenoviruses prior to infection with SAIDS virus have shown a gradual loss of these antibodies as SAIDS progresses and have been found to have no antibody to CMV or simian adenoviruses at death. These results suggest that infection of rhesus monkeys with the SAIDS retrovirus can impair both their ability to mount a primary antibody response to the SAIDS agent and their ability to respond to antigens to which they previously were primed. Radial immunodiffusion studies show that concentrations of IgM, IgG, and IgA antibodies are very low in animals with advanced SAIDS. Histological examinations of lymph nodes of animals with SAIDS have shown diminished numbers of T and B cells in nodes (London WT, Madden DL, Gravell M, et al: Lancet, 1983, 2:869-873). In sum, the humoral immune responses in rhesus monkeys with SAIDS are severly impaired, more so than are the humoral immune responses of humans with AIDS (Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76).

No inversions of T4:T8 helper:suppressor T cell ratios have been found in rhesus monkeys with SAIDS. This is the case regardless of the time after infection or the severity of the disease. In contrast, inverted T4:T8 lymphocyte ratios are common in humans with AIDS (Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76).

Studies of the responses of lymphocytes from rhesus monkeys with SAIDS to stimulation with the mitogens, phytohemagglutinin, concanavalin A, and pokeweed mitogen, have shown that, in the early stages of the disease, lymphocyte responses are not impaired. However, in late stages of the disease, when animals are near death, stimulation indices are significantly lower than are those of controls (Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76).

Using a type D SAIDS retrovirus grown in tissue culture, our collaborators from the CPRC have also transmitted fatal SAIDS to rhesus monkeys (Marx RA, Maul DH, Osborn KG, et al: Science, 1984, 223:1083-1086). Isolations of similar type D retroviruses have been made from macaque species with SAIDS housed at the New England and Washington Regional Primate Research Centers (Stromberg K, Benveniste RE, Arthur LO, et al: Science, 1984, 224:289-292; Daniel MD, King NW, Letvin NL, et al: Science, 1984, 223:602-605). However, transmission studies of SAIDS with viruses isolated from diseased animals and propagated in vitro at these centers have not been described. In 1975, Fine and coworkers (Fine DL, Landon JC, Pienta RJ, et al: J Natl Cancer Inst., 1975, 54:651-658) reported that newborn rhesus monkeys inoculated with MPMV died of an immunosuppressive disease having characteristics similar to those of SAIDS. These reports add credence to our conclusion that SAIDS is caused by a type D retrovirus related to MPMV.

We believe that contaminated saliva and urine may be vehicles for the natural transmission of SAIDS. In recent studies, we have isolated SAIDS retroviruses from saliva and urine of diseased rhesus monkeys and were successful in transmitting SAIDS with such viruses propagated in vitro.

M. Gravell and J. Sever. Infectious Diseases Branch, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20205.

SUPPRESSION OF HUMORAL IMMUNITY IN RHESUS MONKEYS WITH SIMIAN AIDS

Simian AIDS (SAIDS) is a frequently fatal, naturally occurring disease of monkeys of the genus Macaca. Affected animals show signs of profound immunosuppression, can be infected with multiple opportunistic agents, and, in some instances, develop Kaposi's-like sarcoma lesions and other malignancies. We and others have reported that the etiologic agent of SAIDS is a type D retrovirus related to Mason-Pfizer monkey virus.

An enzyme-linked immunosorbent assay employing density gradient-purified SAIDS type D retrovirus as antigen was used to study the effect of SAIDS virus infection on the humoral immunity of rhesus monkeys. Two female juvenile rhesus monkeys, 17½ months of age, were inoculated with purified SAIDS-California virus (IDB-1 isolate). Each was monitored serially during the 2 month course of infection till death. No significant increase in antibody to the SAIDS virus was detected at any time during the course of the disease.

Rhesus monkeys infected with cytomegalovirus (CMV) or simian adenoviruses and having measurable titers of specific antibodies to these agents prior to infection with the SAIDS virus gradually lose these antibodies as SAIDS progresses. At death, no antibody to CMV or adenoviruses is detectable in such animals, suggesting that SAIDS causes a general decrease in humoral immunity.

Many different cell types have been found to be susceptible to infection by the SAIDS type D retrovirus. These include bone marrow cells, T cells from thymus and peripheral blood, fibroblasts, and kidney cells. We are endeavoring to determine the mechanism of humoral immune suppression in animals with SAIDS.

M. Gravell, W. London, G. Scherba, R. Hamilton, and R. Atkins. Infectious Diseases Branch, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20205.

COMPARISON OF THE CAUSATIVE AGENT OF SIMIAN AIDS AND MASON-PFIZER MONKEY VIRUS

We and others have reported that simian AIDS (SAIDS) is caused by a type D retrovirus similar to the Mason-Pfizer monkey virus (MPMV). Features of these two viruses are compared here.

The p27 core antigen of the SAIDS virus isolates originating from diseased monkeys from the California Primate Research Center at Davis has been found to be closely related to the core antigen of MPMV. However, antigenic differences were found between the gp70 polypeptide of the SAIDS-California isolates and the comparable polypeptide of MPMV.

The reverse transcriptase associated with the isolate of the SAIDS-California virus designated IDB-1 has a divalent cation preference of magnesium when tested with the synthetic template-primers poly(rA)·oligo$(dT)_{12-18}$ and poly (rC)·oligo$(dT)_{12-18}$. It has a manganese preference when tested with poly(rC)·oligo$(dT)_{12-18}$. The reverse transcriptase of MPMV has the same divalent cation preferences for these synthetic template-primers.

Our immunoprecipitation and polyacrylamide gel electrophoresis studies have shown that the IDB-1 isolate contains four polypeptides with the same molecular weights (10K, 20K, 27K, and 70K daltons) as those reported for MPMV. The 12K dalton and 14K dalton polypeptides reported for MPMV were not detected in immunoprecipitates of SAIDS virus but were seen in electropherograms of non-immunoprecipitated virus.

These studies provide additional information which suggests that the IDB-1 isolate of SAIDS-California virus is related to, but not identical to, MPMV.

M. Leon-Monzon, G. Scherba, R. Hamilton, W. London, B. Potts, and M. Gravell. Infectious Diseases Branch, Intramural Research Program, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20205.

TRANSMISSION OF SIMIAN AIDS WITH TYPE D RETROVIRUS ISOLATED FROM SALIVA OR URINE

Saliva and urine specimens from rhesus monkeys with simian AIDS (SAIDS) were found to contain a type D retrovirus related to Mason-Pfizer monkey virus (MPMV). The virus has been linked etiologically to SAIDS. Virus isolates from

saliva and urine were shown to have the characteristics of the SAIDS agent in their reverse transcriptase divalent cation preference for synthetic template-primers, production of characteristic cytopathology in Raji cells, and antigenic relatedness to MPMV determined by an enzyme-linked immunosorbent assay and a competition radioimmunoassay. Electron micrographs of parotid tissue from an animal with SAIDS also showed budding particles with type D retrovirus morphology. When a virus isolate from the urine of an animal with SAIDS was grown in tissue culture and subsequently inoculated into two normal juvenile rhesus monkeys, SAIDS developed in both animals. Since saliva and urine of monkeys with SAIDS contain infectious SAIDS viruses, they are likely sources by which the disease is naturally transmitted. Thus, care should be taken to avoid contact between normal and infected animals.

M. Gravell, W. T. London, G. Lecatsas, R. S. Hamilton, S. A. Houff, and J. L. Sever. Infectious Diseases Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20205.

INTERLEUKIN 1 AND INTERLEUKIN 2 PRODUCTION BY PERIPHERAL BLOOD MONONUCLEAR CELLS OF HOMOSEXUAL MEN WITH ALTERED IMMUNITY

Interleukin 1 (IL-1) production has been less intensively studied in homosexual men with AIDS or AIDS-related complex (ARC) than has interleukin 2 (IL-2) production (Ciobanu N, Welbe K, Kruger G, et al: J Clin Immunol., 1983, 3:332-340). IL-1 is produced by mononuclear phagocytes from various sources (Dinarello, CA: Rev Infect Dis., 1984, 6(1):51-95). In patients with AIDS and opportunistic infections, the macrophages appear to function normally when assays involving myeloperoxidase staining, measurements of oxidative metabolism, phagocytosis, and antimicrobial activity are performed (Murray HW, Rubin BY, Masur H, et al: N Engl J Med., 1984, 310:883-889). Generally, IL-1 production has correlated with other parameters of monocyte activation (Dinarello CA: Rev Infect Dis., 1984, 6(1):51-95).

We evaluated IL-1 and IL-2 production in 12 homosexual men who did not have AIDS but who had cutaneous anergy and low levels of T-helper (Th) cells. Four of the patients had weight loss, fatigue, and diffuse lymphadenopathy, while eight were asymptomatic or had chronic lymphadenopathy only. Ten heterosexual men served as controls.

The number of Th cells for the study group was 481 ± 255 (mean ± SD)/mm^3 and the number of T-suppressor (Ts) cells was 827 ± 349/mm^3. Heterosexual controls had 963 ± 333/mm^3 Th cells and 671 ± 303/mm^3 Ts cells. Lymphocyte proliferative responses to two mitogens, phytohemagglutinin (PHA) and concanavalin A, were depressed in homosexual men, but the differences from the results obtained for heterosexual controls were not significant.

The IL-1 production by adherent peripheral blood mononuclear cells stimulated by lipopolysaccharide was measured by a lymphocyte activating factor assay. The results are expressed as counts per minute (cpm) of ^{3}H-thymidine (^{3}H-TdR) incorporated into mouse thymocytes. IL-2 production by non-adherent peripheral blood mononuclear cells induced by PHA was analyzed using a T-cell growth factor assay. Results are expressed in cpm for ^{3}H-TdR incorporated into IL-2-dependent CTLL-20 cells.

Production of both IL-1 and IL-2 was significantly depressed in homosexual men when compared with the production in heterosexual controls (Table). Seven of 12 homosexual men had IL-1 production at a level that was <500 cpm, whereas all heterosexual controls were at a level >3000 cpm. The IL-2 production in seven homosexual men was <150 cpm as compared to >400 cpm in all heterosexual controls. Five participants showed depressed production of both IL-1 and IL-2 (<500 cpm and <150 cpm, respectively).

The IL-2 production was similiar in those homosexual men with Th <400/mm^3 and those with Th >500/mm^3. Four homosexual men with low levels of monocytes (M) (<100/mm^3) had lower IL-1 production (367 ± 449 cpm) than did eight homosexual men with higher levels of M (1212 ± 1736 cpm). IL-1 and IL-2 production were similiar in symptomatic and asymptomatic homosexual men.

Peripheral blood mononuclear cells of homosexual men without AIDS but with evidence of immune dysregulation produce less IL-1 and IL-2 than do cells of heterosexual controls. The decrease in IL-1 production and the recent finding by Kaye and co-workers that IL-1 promotes expression of IL-2 receptors (IL-2R) on T helper cell surfaces in vitro may explain why there is reduced IL-2R expression by stimulated lymphocytes in some patients with AIDS and lymphadenopathy syndrome (Kaye J, Gillis S, Mizel SB, et al: J Immunol., 1984, 133:1339-1345; Prince HE, Kermani-Arab V, Fahey JL: J Immunol., 1984, 133:1313-1317). Many of the opportunistic infections in AIDS patients are caused by intracellular pathogens. Effective control and eradication of these organisms require intact cellular immunity. Further investigations of monocyte and lymphocyte interactions, particularly their mediation by monokines and lymphokines, are therefore warranted in ARC patients, since the deregulation of cellular immunity may be instrumental in the subsequent development of opportunistic infections.

J. Goldsmith, J. Huprikar, S. Wu, J. Chmiel, D. G. Ostrow, and J. P. Phair. Section of Infectious Disease, Department of Medicine and Department of Community Health and Preventive Medicine and Cancer Center, Northwestern University Medical School and the Howard Brown Memorial Clinic, Chicago, Illinois 60611.

IL-1 and IL-2 PRODUCTION

	Homosexual Men with ARC (n = 12)	Heterosexual Controls (n = 10)	
IL-1 production*	1026 ± 1551	6719 ± 4010	p = 0.0002†
IL-2 production‡	281 ± 288	722 ± 232	p = 0.001

* cpm (mean ± SD)/10^6 assay cells.

† Student's two-sample t-test.

‡ cpm (mean ± SD)/10^4 assay cells.

DEFECTIVE FUNCTION OF ANTIGEN-PRESENTING CELLS IN AIDS

In a recent publication, Belsito and associates (Belsito DV, Sanchez MR, Baer RL, et al: N Engl J Med., 1984, 310: 1279-1282) reported that persons with AIDS or the AIDS-related complex had significantly fewer numbers of Ia-positive Langerhans' cells in their skin biopsies than did normal subjects. They suggested that this abnormality might be associated with defective antigen presentation by these cells in the skin and perhaps by other antigen-presenting cells elsewhere in the body.

We have had a unique opportunity to obtain data that support this proposal. One of our male patients with AIDS proved to be HLA-identical to his sister, and cells from these siblings were mutually non-responsive in mixed leukocyte cultures. Mononuclear cells from the patient and his sister were obtained by Hypaque-Ficoll centrifugation of peripheral blood. Cell preparations from both subjects contained 10% monocytes and 90% lymphocytes.

The T cell proliferative responses of the cells were assessed by culturing 2.5×10^5 lymphocytes from each subject in the presence or absence of candida antigen (20 µg protein/ml). After 6 days, the cells were labeled with tritiated thymidine to measure antigen-dependent DNA synthesis. Antigen presentation was assessed by incubating mononuclear cell preparations from each subject with or without candida antigen (20 µg/ml) for 120 minutes at 37°C. The cells were then irradiated (1500 R), washed, and mixed with equal numbers of potential responder cells from the sister. (The low numbers of cells from the patient precluded testing the patient's cells as responders in the second stage of the assay.) In these second stage cultures, therefore, the only antigen involved was that presented by cells from the first incubation. After 5 days, the cells were labeled with tritiated thymidine and harvested.

T cells from the sister responded to candida antigen with a proliferative response as measured by thymidine incorporation, but T cells from the patient did not (Table, part A). In the two-stage studies (Table, part B), antigen-pulsed cells from the sister were able to stimulate the incorporation of thymidine by other (responder) cells from the sister. By contrast, antigen-pulsed

T CELL RESPONSES TO CANDIDA

Experimental Design	Cells from	Candida	cpm	Stimulation Index
A. Antigen present throughout experiment	AIDS patient	–	201	—
		+	241	1.2
	Sister	–	754	—
		+	6183	8.2
B. Antigen presented by antigen-pulsed cells to sister cells in second stage culture	AIDS patient (1° culture)	–	669	—
		+	899	1.3
	Sister (1° culture)	–	1727	—
		+	8927	5.2

cells from the patient did not stimulate a proliferative response by a responder cell preparation from the sister.

The well-recognized immunologic components of AIDS include profound depletion of T lymphocytes, especially helper T cells, and marked immunodeficiency. Our observations and the report that Ia-positive Langerhans' cells are deficient in patients with AIDS raise the possibility of yet another immunologic abnormality—a defect in antigen presentation. The existence of such a defect, if confirmed, could severely limit the efficacy of certain forms of immunotherapy for AIDS patients.

C. H. Kirkpatrick, K. C. Davis, and C. H. Horsburgh, Jr. Conrad D. Stephenson Laboratory for Research in Immunology, National Jewish Hospital and Research Center, Denver, Colorado 80206.

MEDICAL RESEARCH COUNCIL WORKING PARTY ON AIDS

A Working Party on AIDS was set up by the Medical Research Council (MRC) in the United Kingdom (UK) in the autumn of 1983. The mandate for the Working Party was threefold: (a) to review scientific understanding of and research on AIDS in the UK and abroad, (b) to encourage contact and co-operation between researchers in the field, and (c) to advise the MRC as to the current status of knowledge in the field and about topics of interest for research.

The first meeting was held in October, 1983. Clinical, epidemiological, etiological, and pathogenetic aspects of AIDS were reviewed. The Working Party then went on to consider what opportunities for research would be unique or special to the UK. That the epidemic was lagging some 3 years behind the epidemic of AIDS in the United States meant that the background against which AIDS develops might be delineated, and the emergence of AIDS and AIDS-related conditions in high risk groups might be observable. The pattern of disease in the UK seemed somewhat different from the pattern observed elsewhere and needed careful documentation.

The structure of venereology in the UK was considered such that the highest risk group (homosexual men) could be studied in a small number of well-equipped centers with good contact with their communities. The position of gastroenterology in the UK was thought to be such that opportunities would be available for AIDS research. The system for hemophilia treatment and for blood product organization in the UK would make possible detailed studies of hemophilia-associated cases. The organization of epidemiology in the UK was thought well-suited for studying the AIDS problem. The close links between clinical and laboratory workers in immunology in the UK were considered an asset. Finally, it was felt that particular opportunities to pursue carefully controlled and monitored therapeutic trials were available. On the other hand, there appeared to be no unique virology facilities in the UK, nor was there special expertise in genetic engineering that was not available in other countries. The meeting concluded after considering three grant proposals that were to be forwarded to the Systems Board of the MRC for further consideration.

The second meeting of the Working Party was held in December, 1983. Reports from several meetings on AIDS that had been held in various parts of the world were given. The major focus of the meeting involved further discussion of those areas proposed for future research in the UK.

The third meeting was held in April, 1984. A document had been prepared outlining the possibilities for research. Eight conclusions and recommendations were made. (a) The national surveillance system for AIDS, which was based mainly on voluntary reporting of cases, should be extended. (b) Detailed studies of AIDS occurring in hemophiliacs should be carried out. (c) Longitudinal studies of homosexual men attending clinics (particularly St. Mary's and Middlesex Hospitals in London) should be undertaken, and such studies should be continued for at least 3 years. (d) All cases of AIDS should be studied clinically and documented completely, and studies of the pathophysiology of diarrhea and malabsorption should be encouraged. (e) New therapeutic methods should be evaluated by local groups on a few patients in pilot studies and followed up in larger trials if promising results were obtained. (f) All microbiological possibilities for an etiologic agent could not be adequately pursued. Because a viral etiologic agent seemed very likely, groups of workers with enthusiasm and skill for studying candidate viruses should be encouraged to do so. The MRC was already supporting a restriction endonuclease mapping survey of the cytomegaloviruses isolated. In addition, a search was underway for human T leukemia/lymphoma and related viruses and antibodies against them. (g) A good deal of work has already been done on immunological changes in AIDS but not on immunohistopathological changes. The reagents and facilities for studying the latter are excellent in the UK and these studies should be pursued. (h) Useful surrogate tests should be developed for studying blood sample donations.

After the report was considered, three grant proposals were discussed. The meeting was followed by a press briefing. The fourth meeting of the Working Party is scheduled for the autumn of 1984.

Members of this Party are D. A. J. Tyrrell, D. Taylor-Robinson, A. J. Pinching, M. W. Adler, A. L. Bloom, N. S. Galbraith, J. R. W. Harris, P. J. Lachman, H. P. Lambert, K. Murray, J. G. P. Sissons, R. S. Tedder, A. D. B. Webster, and R. Weiss.

D. Taylor-Robinson. Division of Sexually Transmitted Diseases, Clinical Research Centre, Harrow, Middlesex, England HA1 3UJ.

U.S. AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF OCTOBER 1, 1984

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	1475	24	432	29
PCP without KS	3309	54	1659	50
Both KS and PCP	377	6	252	67
OI without KS or PCP	1021	17	559	55
TOTAL	6182	100	2902	47

KS = Kaposi's sarcoma PCP = Pneumocystis carinii pneumonia
OI = Opportunistic infection

	MALES		FEMALES		TOTAL	
PATIENT GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Adult/Adolescent						
Homosexual or bisexual men	4503	78	—	—	4503	73
IV drug user	835	14	226	57	1061	17
Haitian	195	3	35	9	230	4
Hemophiliac	42	1	0	0	42	1
Heterosexual contact†	2	0	44	11	46	1
Transfusions with blood products	42	1	30	8	72	1
None of the above	164	3	64	16	228	4
TOTAL	5783	100	399	100	6182	100
Pediatric‡						
Parent with AIDS or at increased risk of AIDS	21	53	23	79	44	64
Hemophiliac	4	10	0	0	4	6
Transfusion with blood products	10	25	2	7	12	17
None of the above	5	13	4	14	9	13
TOTAL	40	100	29	100	69	100

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.
† With a person with AIDS or at risk for AIDS.
‡ Includes patients under 13 years of age at time of diagnosis.